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SWITZER, JULIET CAROLINE	
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1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/800,322	JAMES ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *2,3,6-8,16-31 and 34-82* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-13 and 32* is/are rejected.

7)☒ Claim(s) *14, 15, 33, and 83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner handling this application has changed. Please address future correspondence concerning this application to Juliet Switzer, Art Unit 1634.

2. Currently, claims 1-83 are pending. Claims 1, 5, 9, 10, 11-15, 32, 33, and 83 are under prosecution. All other claims are with drawn as being drawn to non-elected inventions.

3. The comments regarding the claim to priority are withdrawn in view of applicant's clarification provided in the response received 8/15/07 (see page 22-23 of the response).

Election/Restrictions

4. Applicant's election with traverse of Group I, Claims 1-33 and election of SEQ ID NO; 7 in the paper filed 10/18/2006 is acknowledged.

In the paper received 8/15/07 applicant disagrees with the Examiner's determination of the claims that should be withdrawn from consideration, noting that original group I contained claims 1-33. However, the original restriction requirement also included a further restriction requirement that gave applicant the opportunity to elect a single combination of sequences for examination (p. 6 and following of the restriction requirement mailed 4/14/06). In response, applicant elected the combination which includes the single sequence identified as SEQ ID NO: 7. Therefore, contrary to applicant's assertion, it was proper, and remains proper to withdraw claims which were indicated within group 1 but which require other, non-elected combinations including claim 16 and those claims which depend from claim 16. Should a claim which requires the elected combination become allowable, rejoinder of all methods which recite combinations that require the allowable combination will be considered as appropriate.

Applicant's comments regarding claims 32 and 33 have been considered and are persuasive. These claims are treated with the elected group in this office action insofar as they depends from claim 14 or 15. In response to this office action please change the status indicators as appropriate for these two claims.

Claim Objections

5. Claims 14, 15, 33 and 83 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiply dependent claim. See MPEP § 608.01(n). Claim 14 is multiply dependent and depends from claim 13 which is also multiply dependent. Claim 15 depends from claim 14. Claim 33 is multiply dependent and depends from claim 14 which is also multiply dependent. Claim 83 is multiply dependent and depends indirectly from claim 14 which is also multiply dependent. Accordingly, the claims 33 and 83 not been further treated on the merits.

6. Claim 14 as it is currently written is technically improperly multiply dependent because

7. Claims 1, 5, 9, 10, 11, 12, 13, 14, 15, 32, 33 and 83 are objected to because they recited non-elected subject matter in the alternative.

8. In view of the election of the single sequence of SEQ ID NO: 7, claims 9-12 have all been considered as being identical in scope with regard to the examined invention, and thus are duplicative of one another.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1, 5, 9-13 and 32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1, 5, 9-13 and 32 broadly encompass a method of determining the onset or a predisposition to the onset of a gastrointestinal tract neoplasm in an individual said method comprising measuring the level of expression of SEQ ID NO: 7 or a related nucleotide sequence capable of hybridizing to SEQ ID NO: 7 under "high stringency conditions." The claims set forth that an increase of said nucleic acid molecule relative to the normal level of expression in an individual is indicative of the onset or predisposition to the onset of said neoplasm. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts

such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

"Measuring the level of expression" is understood in light of the specification to be a measurement of transcription or translation of a nucleic acid molecule- that is measuring mRNA products or measuring expressed protein products (p. 23 of specification).

"A nucleotide sequence capable of hybridizing" to SEQ ID NO:7 "under high stringency conditions," encompasses many nucleic acids that would hybridize to SEQ ID NO:7 or its homolog or a variant or a homologue or a splice variant of SEQ ID NO: 7.

"Individual" is a broad term that includes human, dog, cat or other higher animals. However, whether all these animals have the SEQ ID NO: 7 or its related nucleic acid as set forth in the instant claims is not clear. The specification teaches a sequence with the asserted function as a neoplasm marker in human but not in any other individuals.

"Biological sample" is a broad term that includes any sample of biological material including urine, hair, prostate, breast, as well as blood, serum, saline solution extracted from the lung following lung lavage or the solution retrieved from an enema wash. However, the specification does not teach overexpression of SEQ ID NO:7 functional derivatives, any variants or homologs of SEQ ID NO:7 in any other tissue except colorectal tissue obtained from colonoscopy. The specification teaches the sequence is from a human colorectal biopsy sample (page 97, line 4) but does not teach any other source in human and any source of sampling in other non-human individuals that this sequence is overexpressed in other neoplasms.

The onset of "gastrointestinal tract neoplasm" is a understood in view of the specification to be a reference to one or more cells of that individual exhibiting abnormal growth characteristic

(specification page 41), and neoplasm also encompasses any abnormal and uncontrolled growth of tissue in an on any types tissues and organs. Thus, the claimed methods encompass methods for determining the onset or predisposition for even a single cell to have abnormal growth- whether that growth be benign or malignant. However, the specification only teaches overexpression of the SEQ ID NO: 7 sequence in colorectal adenoma which is a benign tumor of epithelial origin which is derived from glandular tissue (p. 1 of specification). The specification does not teach overexpression of SEQ ID NO:7 functional derivatives, variants or homologs in colorectal neoplasm or SEQ ID NO:7 and its related nucleic acids in any other types of neoplasms encompassed by the instant claims- for example, the specification does not show that SEQ ID NO: 7 is overexpressed in adenomas of the stomach or that SEQ ID NO: 7 is overexpressed in adenocarcinomas both of which are encompassed by the instant claims. The specification teaches the adenoma biopsy samples from human patients with adenomas undergoing colonoscopy. The specification does not teach any other source in human or other types of adenoma and any source of sampling or types of adenoma in other non-human individuals. Many transcripts are tissue- and tumor-specifically expressed at different levels. For example CD44v expression level is high in all metastatic brain tumors but virtually negative in tumors metastatic to the spine (Resnick et al., 1999, Molecular Diagnosis, 4: 219-232).

Furthermore, the term "gastrointestinal tract" is quite broad encompassing all parts of the tract including the entire digestive canal from mouth to anus including esophagus, stomach, duodenum, ileum, large bowel, and rectum.

Each of the dependent claims recites a further limitation, for example, wherein the nucleotide sequence is SEQ ID NO: 7, wherein the subject of detection is the expression product

of said nucleic acid sequence, wherein the neoplasm is colorectal neoplasm, or in particular adenoma, and wherein the adenoma is a tubular adenoma, tubulovillous adenoma, or a villous adenoma, but all of these claims still encompass breadth and subject matter which is problematic and discussed in this office action.

Guidance in the Specification and Working Examples

The examples in the specification teach differential display analysis of samples of adenoma and normal tissue obtained from patients undergoing colonoscopy, comparison of the isolated sequences to nucleic acid databases housed by NCBI using BLAST, and RT-PCR confirmation of the differential expression of the isolated molecules (examples 1-3). Example 4 describes the testing of 71 colon adenoma tissue samples by quantitative RT-PCR and comparison of the expression levels to the mean expression levels of normal tissues. From these results a "fold increase" was tabulated for each isolated nucleic acid. The specification teaches on page 79, Table 2 that SEQ ID NO: 7 corresponds to Adenoma Marker clones named 12-2f and 8-2d. The specification does not teach how SEQ ID NO: 7 is related to the inserts from these clones nor does the specification disclose how the inserts in the clones are related to one another.

Table 3 from the specification teaches that clone 8-2d was, on average, upregulated 50 fold relative to the mean expression levels of normal tissues, and that clone 12-2f was on average, upregulated 45 fold relative to the mean expression levels of normal tissues (table 3), and that both clones were upregulated greater than 5-fold in 100% of the adenoma tissues (table 5). The specification also teaches, however, that 19% of the normal tissue samples showed upregulation of both of these clones (table 6 and table 7).

The specification repeatedly refers to clones 8-2d and 12-2f as being different clones, with these two clones presenting with different results in Table 1 and as part of different groups

of diagnostic markers in Tables 9-15, but the specification is silent as to how the two clones are actually related, or what the sequence of the insert of the individual clones are or how these clones relate to SEQ ID NO: 7.

There is no external working example which validates the use of SEQ ID NO: 7 as a marker for colorectal adenoma.

The data given in the tables is given as averages- the mean fold increase in adenoma samples versus the mean expression level of normal tissues. The specification is silent as to the number of normal tissue samples that were used to obtain the mean value for normal tissues. For both normal and adenoma means, no mention is given in the specificaiton as to the ranges of observed values, the variation among samples or any formal statistical analysis to determine if the differences observed between types can be attributed to sample effects of to the chance of error. This is a significant absence given that the specification teaches that 19% of normal tissues also over expresses both clones.

The specification does not provide any evidence that an increased expression of SEQ ID NO: 7 related sequences (that is sequences which hybridize under "high stringency" to SEQ ID NO: 7 but are not 100% identical to SEQ ID NO: 7) can be used as a marker for the presence of colorectal adenoma in colon tissue samples.

The specification does not teach that SEQ ID NO: 7 can be used as a neoplasm marker for all types of gastrointestinal neoplasms in all species of individuals using any possible type of biological sample. The specification exemplifies that clones 8-2d and 12-2f have levels of expression higher than five fold versus average expression in normal control tissue in 100% of adenoma tissues, but the specification does not demonstrate that high levels of expression could be observed in other types of tissues- blood or urine or stomach tissues- or even that if it were that it would indicate colorectal adenoma or any other type of adenoma or neoplasm. human patients with colorectal adenoma (Examples I). However, the specification does not teach any

other examples in any other tissue, neoplasm or nucleic acids comprising of SEQ ID NO: 7 sequences with deletions, additions, substitutions and variants, homologues, functional derivatives or guidance as to what sequences or features of SEQ ID NO: 7 sequences or its variants, homologues, functional derivatives sequences would hybridizes to SEQ ID NO: 7 and would meet all the limitations of the instant broad claims where such a nucleic acid can be used to determine the onset or a predisposition to the onset of any neoplasm in any individual by measuring elevated expression levels of the sequence.

Further, the claims are drawn to encompass determining a predisposition to the onset of gastrointestinal tract neoplasm. The specification, however, only demonstrates overexpression of the subject clones in actual colorectal adenomas. The specification does not demonstrate that expression of these clones increases prior to the presence of the adenomas in the colon or rectum.

The specification does not demonstrate the detection of SEQ ID NO: 7 translation products, nor does it demonstrate that these putative translation products are detectable at different levels that could be used as set forth in the claimed methods.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

The unpredictability of the art and the state of the prior art

It is highly unpredictable whether sequences which hybridize to instant SEQ ID NO: 7 under "high stringency" conditions will also be markers for colorectal adenoma. High expression of Prostate specific membrane antigen (PSMA) in more aggressive prostate cancer makes PSMA a potential diagnostic target for prostate cancer (Schmittgen et al., Int. J. Cancer, 2003, 107:323-329). PSMA has three alternatively spliced variants, PSM', PSM-C and PSM-D. When PSMA and the alternatively spliced variant levels were compared by qPCR methods in various samples of normal, benign, primary and metastatic tissues from much larger sample size

of 72 patients, however, the results indicate complex and contradictory expression profiles of the splice variants quite different from the initial PSMA expression patterns (Table III). For example although PSMA mRNA levels were seen increased 3-fold in primary prostate tumor, bone and lymph node metastases samples compared to normal prostate it was not increased in liver metastases samples but in fact decreased slightly. Therefore an increased PSMA mRNA expression level may be a marker for prostate tumor, bone and lymph node metastases but not for liver metastases. Additionally, not all PSMA variant transcripts showed increased expression levels in prostate tumor as the splice variants PSM-D expression level is not increased but rather decreased. PSM-D mRNA level, on the other hand, is increased in other types of tissues such as bone and lymph node metastases samples. Therefore the art teaches the use of a marker for disease risk assessment is unpredictable depending on the variants, biological sample and sources, and types of neoplasm.

Because the claims encompass the analysis of translation products of SEQ ID NO: 7 or translation products of nucleic acids that hybridize to SEQ ID NO: 7 under high stringency while the specification provides only an example of the analysis of mRNA levels by differential display and quantative RT-PCR, it is relevant to point out the unpredictability as to whether or not a measure of any nucleic acid expression is indicative of the level of protein in a sample. The post-filing art of Chan teaches that cells have elaborate regulatory mechanisms at the level of transcription, post-transcription, and post-translation (p.1, last paragraph), and that transcript and protein abundance measurements may not be concordant (p.3, sixth full paragraph). Thus it is unpredictable as to whether or not the results pertaining to nucleic acid expression, as

presented in the instant specification, would be applicable to methods requiring or encompassing the analysis of a protein samples.

Given the breadth of the claimed method as encompassing the examination of samples from any organism, it is relevant to point out that Hoshikawa et al (2003) teaches unpredictability with regard to applying gene expression results among different organisms. The reference teaches the analysis of gene expression in lung tissue in response to hypoxic conditions which lead to pulmonary hypertension (Fig. 1). The reference teaches that the gene expression profile in mouse is different from that observed in rat (Tables 1-4; p.209 - Abstract). Thus it is unpredictable as to whether or any genes that are sepsis related in humans are in fact applicable to diagnosing a condition of sepsis in any other non-human organism. There is no evidence on the record that SEQ ID NO: 7 is present in other organisms or that it is differentially expressed in colorectal adenoma tissues in other organisms.

There is no evidence on the record which demonstrates that SEQ ID NO: 7 is indicative of any other type of neoplasm other than colorectal adenomas. There is no evidence on the record that there is a universal gene expression pattern for all adenomas of the gastrointestinal tract or all neoplasms of the gastrointestinal tract. Ostensibly, each type of abnormality would have a unique expression profile, and it is highly unpredictable as to whether or not SEQ ID NO: 7 would be sufficient to suggest the presence of any abnormality other than colorectal adenoma.

Even if the claims were limited to determining the overexpression of SEQ ID NO: 7 in a human patient wherein the sample is a colorectal biopsy, and the claims were amended to recite a method for detecting the presence of colorectal adenoma because the actual data given in the specification is not enough to apprise on of skill in the art with particularity as to how to practice

the invention. That is, there no guidance or showing that demonstrates the range of values observed in the adenoma versus normal samples, and the specification teaches that at least 20% of the normal samples overexpressed the subject clones. It is highly unpredictable, therefore, what level of expression of SEQ ID NO: 7 must be observed in order for one to successfully conclude that adenoma is present or more likely than not present. In order to use the claimed invention, in any embodiment, one would have to undertake an extensive amount of unpredictable experimentation.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied such as detection of elevated expression of SEQ ID NO: 7 functional derivatives, variants, functional derivatives, homologs and other SEQ ID NO: 7 sequence-related nucleic acid molecules with all types of gastrointenstinal neoplasms in all types of individuals that meets the limitations of the instant claims and determine if each sequence expression level increase in all types of patients and tissues can be used as a marker for the onset or a predisposition to the onset of any neoplasm in any individual. Furthermore, one would have to discover the expression product or products of SEQ ID NO: 7 and establish reliable methods of detection and that this product is in fact translated in patterns similar to the transcription patterns of the observed mRNA. This would require extensive experimentation and specific guidance, with many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps, which are not routine, and an artisan of skill would not have known at the time of invention.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where an increased expression of a DNA marker is asserted to be associated with gastrointestinal neoplasma of any type, the specification provides minimal guidance for a specific example (the expression levels of two clones in colorectal adenoma tissue) and no guidance to support the limitation of the instant claims wherein overexpression of any SEQ ID NO: 7 functional derivatives, variants, functional derivatives, homologs and other SEQ ID NO: 7 sequence-related nucleic acid molecules can be used as a neoplasm marker.

Further, the prior art and the specification provides insufficient guidance to overcome the art recognized unpredictability of different expression patterns for splice variants. Therefore the use of splicing variants are unpredictable as marker sequences. for all types of neoplasms in various tissues and sample sources. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1, 13, and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are broadly drawn to a method of determining the onset or a predisposition to the onset of a neoplasm in an individual comprising measurement of the level of expression of a nucleic acid, (a) comprising SEQ ID NO:7; (b) any nucleic acid sequence capable of hybridizing to SEQ ID NO:7 under high stringency conditions. The broad genus encompassed by the claims includes the recited nucleic acids of any species such as rat, dog, cat, etc., as well as SEQ ID NO: 7 variants, functional derivatives, homologs and other SEQ ID NO: 7 sequence-related nucleic acid molecules.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that Vas- Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In The Regents of the University of California v. Eli Lilly (43. USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B (1), the court states that "An adequate written description of a DNA. . .' required a precise definition, such as

by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention.

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure.

With regard to "individual", the specification does not teach any structure of SEQ ID NO:7 in dogs, cats and in other organisms, nor does it provide any guidance as to the structure of such sequences in other individuals other than to the sequence from human colorectal tissue.

With regard to "a functional derivative, variant or homologue", the specification does not teach any structure of a DNA sequences that would be a functional derivative, variant or homologue of the human SEQ ID NO:7 or a sequence that hybridizes to SEQ ID NO:7 under a low stringency conditions, in any individual, nor does it provide any guidance as to the structure of such sequences in any individual. Many alternative splicing variants, for example, encode proteins with vastly different function, localization and expression. Two functionally disparate PSMA and PSM' polypeptides with differential cellular localization are generated from the protein-coding sequences of the same gene. The expression levels of the two functional derivatives from splicing variants of the same gene are different depending on tissue-type and tumor-type as explained above (Schmittgen et al., page 323, right column, paragraph 1). Therefore, sequence variants or homologs may have vastly different functions and expression patterns and levels and therefore may not be used as markers for the same biological functions such as onset or predisposition of neoplasm. In addition, functional derivatives of PSMA alternative transcripts as described above exemplify that functional derivatives have tissue- and

tumor-specific expression levels. For example, translation of PSM-C mRNA results in a protein that is identical to PSM' and therefore with identical function; however, the expression levels of the two transcripts are quite different. The expression levels of bone metastases PSM-C is increased approximately 2-fold but the identical transcripts that encode identical proteins is seen decreased in the samples. Therefore even two transcripts that encode identical proteins with identical function can have differential expression patterns depending on tissue and tumor types.

With regard to "a nucleotide sequence capable of hybridizing to any one or more of the sequences" of SEQ ID NO:7 "under high stringency conditions", the specification does not teach any structure of a DNA sequences that would hybridize to SEQ ID NO:7 under the recited high stringency condition in any individual, nor does it provide any guidance as to the structure of such sequences in any individual. The specification has not discussed any structural features which are essential for such a molecule to .

Next, it is determined whether other identifying characteristics have been described that will describe other members of the genus. In the instant case none of the identifying characteristics that would identify potential related nucleic acid markers as neoplasm markers have been described other than the primary structure of SEQ ID NO: 7. The specification teaches the human sequence SEQ ID NO: 7 but no identifying characteristics that can be used to identify other sequences encompassed by the broad instant claims as neoplasm marker when overexpressed. Therefore, the specification does not teach any relevant identifying characteristics of a representative number of species within the claimed genus to identify a nucleic acid sequence when overexpressed can be used as a neoplasm marker.

Applicant is clearly in possession of SEQ ID NO: 7.

The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics of SEQ ID NO: 7 in other organisms and sequences or features of sequences comprised of SEQ ID NO: 7 that identify members of the genus, and because the genus is highly variant, and the specification fails to describe specific species of the genus of the neoplasm marker in non-humans and other sequences in human than the single species of SEQ ID NO: 7 disclosed and without any guidance to structure/function relationship to determine if a nucleic acid identified would be a useful neoplasm marker, one of skill in the art would conclude that applicant was not in possession of the claimed genus.

Response to Remarks

The rejections under 112 1st paragraph have been modified to address the amended claims. In addition, the lack of enablement rejection has been expanded and further explanation is provided. The issue regarding lack of enablement was not fully appreciated in the previous office action. Any inconvenience is regretted.

Applicant argues on page 27 of the remarks that the amendment to the claims removes the issues related to 112 1st paragraph. This is not persuasive given the remaining breadth of the claims. Even under high stringency conditions SEQ ID NO: 7 (which is over 3,000 nucleotides in length) still would be expected to hybridize to sequence variants which may or may not be overexpressed in colorectal adenomas, and genus which potentially includes splice variants, allelic variants and mutants as well as related sequences. There is no discussion in the specification as to which portions of SEQ ID NO: 7 can be modified yet still the molecule will retain its functionality as a potential marker for colorectal adenoma.

Applicant argues on page 26 that one skilled in the art would be able to determine a suitable cellular source for the use in determination. However, this is not persuasive. The specification clearly encompasses, for example, the use of a myriad of cellular sources, yet there is no experimental data showing that any tissue except adenoma tissue itself overexpresses SEQ ID NO: 7. It is highly unpredictable, for example, whether blood could be used as a marker for colorectal adenoma since it is not clear if the effect of the presence of the disease is global such that expression in blood cells would be the same as that in the tumor itself. For each different sample type, separate experimentation would be required to establish the validity of the method, until it became clear that universal relationships exist, if such a time ever occurred. Furthermore, applicant's comments on page 26 that protein products secreted into blood could be tested. There is no evidence in the prior art or in the specification that SEQ ID NO: 7 is translated into a protein product in adenoma cells or any cells, nor that this putative protein product is secreted into the blood, nor that if it is it is detectable in the blood at any level that is useful for determining the onset or predisposition to adenoma.

The prior art rejections are withdrawn in light of the amendments to the claims and applicant's comments regarding priority in the third full paragraph on page 27 of the remarks.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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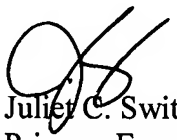

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Art Unit 1634

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